



mobile Patient Reported Outcomes (mPRO™)

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1. Introduction

The FDA defines a patient reported outcome (PRO) as “a measurement of any aspect of a patient’s health status that comes directly from the patient, i.e. without the interpretation of the patient’s responses by a physician or anyone else” (FDA, 2006). Many clinical drug trials nowadays require the collection of PRO data from large numbers of patients. In some trials, PRO data are the only form of data available to assess the effects of the drug being tested. The relative advantages of electronic PRO (ePRO) with respect to paper diaries have been well documented in a number of publications, some of which are briefly reviewed in section 2 below.

t+ Medical, a company spun out from the eHealth and Biomedical Signal Processing group at the University of Oxford, has been developing mobile phone solutions for the self-management of long-term conditions (LTCs) since 2002. This was the year of the launch of data services for mobile telephony in the UK and Europe. The LTC products from t+ Medical all incorporate eDiaries and they have been validated in more than 20 clinical trials of patients with asthma (Ryan et al., 2005), Chronic Obstructive Pulmonary Disease – COPD (Garland et al., 2007), diabetes (Farmer et al., 2007) or hypertension (Fischer et al., 2007). The mobile phone eDiary has also been used successfully by patients undergoing several cycles of chemotherapy for colorectal cancer (Weaver et al., 2008).

As of April 2008, t+ Medical is one of the approved telehealth suppliers to the UK Government’s Whole-System Demonstrators for Telehealth and Telecare. Following the success of its LTC products, t+ Medical has now adapted its core eDiary technology to make it compliant with the regulatory requirements of clinical trials. This has led to the creation of mobile Patient Reported Outcomes (mPRO™), an efficient, flexible and real-time ePRO solution based on an every-day device, the mobile phone. This new system for patient-reported outcomes has a number of significant advantages with respect to conventional ePRO, and these are discussed in section 3 of this paper.

2. Review of ePRO versus paper

The key advantage of ePRO versus a paper diary is that the data acquisition can be date- and time-stamped, so that any retrospective (or forward) completion of the diary cannot occur, as it often does with paper diaries (Stone et al., 2002; Byrom, 2006). This means that there are no queries on diary data and hence there is no need for double data entry or data cleaning. Other advantages (Raymond and Ross, 2000) are as follows:

- Greater subject compliance because of ease of entry of data
- Enhanced data integrity because of internal validity checks (for example, checking for out-of-range data)
- Possibility of interim access to diary data.

In addition, eDiary solutions offer considerable financial benefit: case studies have shown that they reduce costs by 40%, on average, with respect to paper diaries (Mussina, 2005). This is because the patient data collected by ePRO systems have much lower variance than comparable data collected on paper. Hence studies can be powered with fewer patients, saving significant time and cost. Although the hardware costs of electronic solutions are obviously higher, the overall costs of the trial when all activities and materials are taken into account are significantly lower (Mussina, 2005).

3. What is mPRO™?

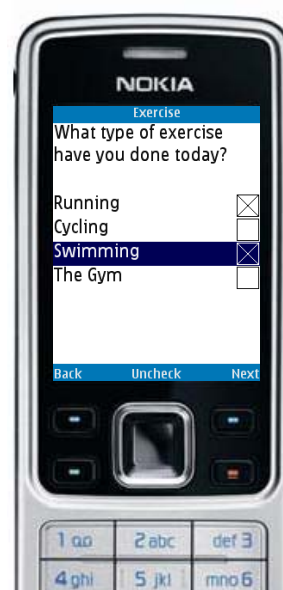
mPRO™ is a logical development of ePRO, which retains the advantages of an eDiary solution, but is based around the mobile phone, an every-day device with which people throughout the world are familiar. mPRO™ offers the pharmaceutical and medical industries a real-time, easy-to-use data capture solution for clinical trials. It allows researchers and their staff to review and analyse the patient data via a webpage /dashboard defining the protocol's Key Performance Indicators (KPIs). The diary can be built within 24 hours (non-validated version) which makes the clinical trial set-up very quick. From receipt of a draft protocol and diary questionnaire, deployment for the start of the trial can be achieved within 15 days. Familiarity with mobile phones and their keyboards makes it easy for patients to complete diaries in their own language. The low cost of a mobile phone with respect to a PDA means that it can be treated as a disposable item, and retained by the patients at the end of the trial, if they so wish.

3.1. Description of system



The overall system is shown in the above block diagram. The main steps in its use, from the moment a new trial is agreed to database lock, are described below:

- a) A secure server is set up as soon as the trial is commissioned. The t+ Medical Clinical Project Manager works with the sponsor company to define the diary and dashboard requirements and complete a specification form. This is then submitted to the t+ Medical development team who build the diary and dashboard. The latter undergo several iterations of User Acceptance Testing, both internally and by the sponsor.
- b) Once the questionnaire has been validated and approved by the sponsor company, t+ Medical converts it to an eDiary template. mPRO™ handsets and data Subscriber Identity Module (SIM) cards can then be provisioned by t+ Medical. (A SIM card is a small electronic card inserted into mobile phones that provides a unique ID to the handset.) The handsets with the trial questionnaire loaded into them (eDiary) and the SIM cards are part of the trial package to ensure a uniform approach and consistency across the board. The eDiary can be loaded into the handsets either locally at each trial site or by downloading the software onto the phones over the air. After final approval, the mPRO™ solution will normally be deployed to the investigational site one week prior to the start of patient enrolment.
- c) After the trial has started, the local investigator sites add patients and record a unique identification number for each one. This number, as well as the ID of the patient's mobile phone, is entered by the investigators logging on remotely onto the trial's webpage/dashboard (see g) and i) below for examples of typical screens).
- d) Using the mobile phone loaded with the eDiary, patients enter and securely submit their data in seconds. Diaries use adaptive branch logic and are designed specifically to provide the desired information in the most relevant format, for example: numeric, multiple choice, check boxes and sliding scales including Visual Analog Scales (VAS – see section 3.1 below), Box Scales, and Numeric Rating Scales. Diary questions can also be provided in different languages. The screen shot (from an eDiary on a mobile phone) on the left below shows a question with a numeric answer (with decimal point control) and the one on the right questions for which multiple answers are possible.



- e) The mPRO™ application also has the capability to receive wireless medical device data from devices such as glucometers, spirometers, weighing scales and blood pressure monitors. The data from these measurement devices are transferred automatically to the phone via Bluetooth, which ensures no transcription errors and hence 100% data integrity (including date- and time-stamping). Typical devices are shown below:

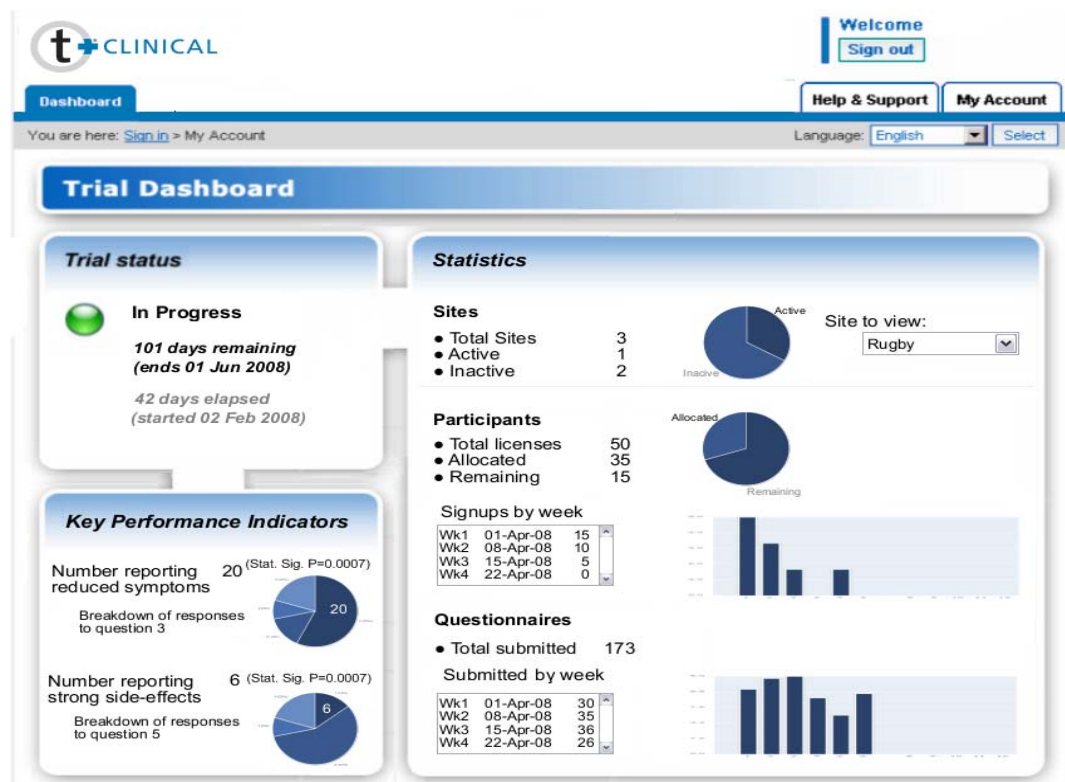


- f) The subject diary answers (and any medical device measurements) are transmitted automatically to the trial server by the software application running on the mobile phone, as soon as the diary is completed. No clinical data therefore reside on the phone, only the questions in the eDiary. Should the phone be lost by the subject (or stolen), no data would be lost.
- g) A unique secure login is provided to Clinical Research Associates (CRAs) and Principal Investigators, giving them access to a Trial Centre Dashboard on a secure web page. This dashboard provides visibility down to the level of an individual patient (see typical screen below). This allows CRAs and Principal Investigators to review real-time measurements (e.g. blood glucose, peak flow or blood pressure data) as well as the diary information submitted by the subjects.

The screenshot shows the t+CLINICAL web application interface. At the top, there is a navigation bar with 'My Account', 'Participants', 'Support', and 'Site' buttons. Below this, the user is logged in as 'Irma Bamble'. The main content area displays a 'Chart for Irma Bamble' with a 'Report' dropdown set to 'Event List'. The 'Date Range' is set to 'Last 30 days', and the data is filtered from '20 May 2008' to '19 Jun 2008'. An 'Event List' table shows a series of 'tPlusDiaryDemo' events. A modal window is open for the event on 'Wed 18 Jun 2008 06:56', containing a form for data entry. The form includes a dropdown for 'Select a demo diary' (Diabetes Demo), a text input for 'How long is it since you last had a meal?' (More than 8 hours), a text input for 'Enter your Blood Glucose Reading' (32.0 mmol/L), a text input for 'Enter your BP reading' (12 mmHg), another text input for 'Enter your BP reading' (10 mmHg), and a text input for 'How much exercise will you do today?'. There are 'Done' and 'Print' buttons at the bottom of the modal.

Date	Time	Summary
Wed 18 Jun 08	08:07	tPlusDiaryDemo
Wed 18 Jun 08	08:07	tPlusDiaryDemo
Wed 18 Jun 08	06:56	tPlusDiaryDemo
Wed 18 Jun 08	06:55	tPlusDiaryDemo
Wed 18 Jun 08	06:54	tPlusDiaryDemo
Tue 17 Jun 08	15:11	tPlusDiaryDemo
Tue 17 Jun 08	09:42	tPlusDiaryDemo
Mon 16 Jun 08	17:02	tPlusDiaryDemo
Mon 16 Jun 08	16:54	tPlusDiaryDemo
Mon 16 Jun 08	16:42	tPlusDiaryDemo
Mon 16 Jun 08	16:28	tPlusDiaryDemo
Mon 16 Jun 08	16:28	tPlusDiaryDemo
Mon 16 Jun 08	16:26	tPlusDiaryDemo
Mon 16 Jun 08	15:59	tPlusDiaryDemo
Mon 16 Jun 08	15:58	tPlusDiaryDemo
Mon 16 Jun 08	15:57	tPlusDiaryDemo

- h) Real-time tracking of KPIs provides the investigators with real-time outcome data and helps to ensure high compliance. Subjects who are not entering data are automatically identified, enabling appropriate action to be taken. Non-compliance alerts are automatically generated for trial personnel via web reports, mobile phone or SMS messaging, if required.
- i) The sponsors are also able to log in to the trial server and obtain restricted, anonymised information made available on the trial dashboard which allows them to check the progress of the trial at every site and overall. The dashboard, shown below, constantly updates, allowing sponsors to monitor at any time the status of the trial.



- j) The dashboard has different levels of permissions associated with the different users. The Principal Investigators remain in control of eSource data in compliance with 21 CFR 312.62 via the dashboard. Clinical trial staff can communicate securely, from the web, directly to their patients through the t+ Clinical encrypted messaging system. Messages that are sent to trial subjects are logged for audit purposes.
- k) At the end of the trial, the Principal Investigators notify the CRAs and subjects via e-mail and SMS messages. The phone software also informs the subjects that the trial is closed and disables the eDiary. All the data (both clinical and meta data) are exported for statistical analysis and the trial server is sent to the client. The data are provided in Clinical Data Interchange Standards Consortium (CDISC)-compliant format.

3.2. Visual Analog Scales for mPRO™

The Visual Analog Scale (VAS) is a validated, self-report measure of pain intensity which, for paper diaries (pVAS) normally consists of a 10 cm (100 mm) horizontal line anchored at both ends (No pain at one end, Maximum pain at the other). Providers of ePRO solutions have implemented electronic VAS (eVAS) on PDA screens, with subjects making entries on the touch-sensitive screen with a stylus. Although the screen is usually 50 mm-wide and hence the line is shorter by a factor of 2, patients cannot mark outside the line and, as with other eDiary entries, the data are transmitted automatically.

In a study comparing the use of pVAS and eVAS by healthy volunteers (Jamison et al., 2002), the overall correlation between ratings of both sensory and cognitive stimuli was found to be $r = 0.91$. Multivariate analyses carried out by the same team showed equivalent stimuli to be rated almost the same whether entered on paper VAS or PDA electronic VAS (with a p value of < 0.00001). The study concluded that switching to an electronic method of collection is not expected to alter the psychometric properties of a scale or questionnaire. The mode of collection (pVAS or eVAS) has no biasing effect on the data collected (Raymond and Marino, 2005).

Mobile phones are more compact than PDAs, hence the screen width is smaller (typically 30 mm rather than 50 mm). As against this, mobile phones are used by a much greater proportion of the population and so many subjects will already be comfortable with their use. Tiplady et al. (2008) have recently carried out an evaluation of the use of a mobile phone to administer Visual Analog Scales, which came out with very positive results.

The scale of the mobile phone which they used was 21 mm wide. When first used by a subject, the mobile phone's VAS scale appeared without a cursor, to avoid bias (Palmbad and Tiplady, 2004). With a PDA, the cursor can appear in the position first tapped with the stylus, but this approach is not available for mobile phones. The scale was instead left initially blank, with no cursor visible. The first response by the study subject was made by pressing on the left or right key. The cursor appeared $\frac{1}{4}$ or $\frac{3}{4}$ of the way across the scale depending on which key was first pressed. The cursor position was then adjusted by the subject using the right and left keys. In this evaluation study (Tiplady et al., 2008), the scale used was a 26-point scale (including 0 and 100), moving in intervals of 4% of scale length.

The conclusions from the Tiplady et al. (2008) study were as follows: (i) the 21 mm mobile phone Visual Analog Scale was as sensitive as the 100 mm paper scale in detecting subjective effects of alcohol; (ii) there was very good agreement between the pVAS method of assessing alcohol effects and the eVAS method implemented on a mobile phone screen of 21 mm-width (intra-class correlation = 0.96). The authors therefore concluded that VAS methods are little affected by scale length over a wide range of scales, supporting the use of portable implementations of these scales on mobile phone screens.

The handsets used in the t+ Medical mPRO™ solution are of a more recent design than those evaluated in the Tiplady et al. study. With the mPRO™ handsets, there are 220 pixels available to define the horizontal, Visual Analog Scale. The available pixels can be divided into 10 units (22 pixels per unit), 25 units as in the Tiplady et al. study (8 pixels per unit) or 50 units (4 pixels per unit), depending on the quantisation of the scale which is required. Again the phone's right and left keys are used to move the marker right or left along the horizontal line.

The screenshot on the left below shows a VAS scale on an mPRO™ phone screen, with descriptive labels at the extremes of scale. The screenshot on the right is an implementation of a Numeric Rating Scale (NRS), with 11 boxes from “No pain” to “Maximum Pain”.



3.3. Advantages of mPRO™

The benefits of mPRO™ should be clear from the description of the system in section 3.1 of this paper, but the list below is a more explicit statement of these benefits:

Simple and quick roll-out: the time to roll-out is as short as it can possibly be. The use of mobile phones ensures that the set-up and roll-out phases are fast: handsets are provisioned to patients within days of diary customisation and completion. Quicker trial implementation leads to results being available more quickly. Diary modifications can be completed and provisioned within 24 to 48 hours. Many of the logistical problems associated with the use of PDAs, such as the distribution, maintenance and recovery of devices (Raymond and Ross, 2000), are minimized, if not eliminated, as a result of the use of mobile phone technology.

Ease of use by patient: The mobile phone is a consumer-quality, robust, familiar device, which the patient can retain at the end of the trial (i.e. it is treated as a disposable item). A mobile phone is much cheaper than a PDA. In addition, the ubiquity of the mobile phone ensures that there is no need for training to familiarise the subjects with the use of the technology, as with PDAs (Raymond and Ross, 2000). The mPRO™ user interface has been developed with an intuitive design to provide easy navigation that enhances the user experience, which positively impacts adoption and on-going compliance.

Bluetooth device connectivity: The mPRO™ application has the capability to receive wireless medical device data from compatible Bluetooth devices, such as glucometers, spirometers, weighing scales and blood pressure monitors. Bluetooth transmission of patient data to the mobile phone guarantees the highest level of data accuracy and integrity.

No data loss: The eDiary *questions* are stored on the mobile phone; the patient’s answers are transferred in real time to the trial server, where they are securely stored. No data is lost if the patient’s phone is stolen or lost.

Real-time data capture and Key Performance Indicator (KPI) reporting: A unique, secure login gives access to the trial dashboard, on which the progress of the trial can be monitored by reviewing KPI information such as recruitment, compliance and data submission rates. The dashboard continuously updates automatically, allowing authorised staff, investigators, monitors, and site coordinators to monitor primary outcomes and data in real time. Active, real-time compliance monitoring leads to high-integrity data (date- & time-stamped).

Secure messaging: Whenever required, authorised staff can communicate securely with study patients through mPRO™'s encrypted messaging system.

Adding subjects and adaptive diaries: Protocol amendments to the original diary can be deployed easily to the trial population, either individually or in batch mode. After the required modifications have been made to the software resident on the t+ Clinical server, all eDiaries can be updated remotely with no disruption to the subject. t+ Medical will retain all versions of the diaries and manage the change control process.

4. Evidence for mPRO™

t+ Medical is the first successful provider of mobile phone technology for clinical trials, primarily because it has spent the past five years developing, testing and refining the same core technology in the context of disease management. Thus mPRO™ is built on a track record of more than 20 clinical studies or trials carried out by t+ Medical in disease management since 2003. These studies have involved the use of eDiaries and Bluetooth-enabled medical devices in the management of long-term conditions such as diabetes type 1 and type 2, asthma, COPD and hypertension.

Highlights from these trials include:

- 0.62% reduction in HbA1c after 9 months in people with Type 1 diabetes (Farmer et al., 2005);
- 31% reduction in uncontrolled use of reliever inhaler in people with asthma (Ryan et al., 2005; Cobern, 2007);
- reduction in hospitalisation rate from 1.64 per annum to 0.70 per annum for COPD patients (Garland et al., 2007);
- Mean/Standard Deviation of systolic Blood Pressure significantly lowered at six months (129.3/16.2 vs 137.3/19.3 mmHg, $p < 0.01$) in a hypertension study with stroke patients (Fischer et al., 2009)

As a result of the large number of disease management trials carried out with hundreds of long-term condition patients, t+ Medical has acquired considerable know-how in the use of mobile phone technology for clinical purposes. This includes:

- secure downloading, over-the-air, of mobile phone applications software from a trial server
- implementation of a wide range of electronic diaries on mobile phones
- encrypted, real-time data transmission from mobile phone to trial server
- real-time compliance monitoring and alerting from processing of data on trial server
- automated, or semi-automated, messaging from server to mobile phone

It is this know-how which has underpinned a range of reliable, robust and clinically-proven LTC products and which now forms the basis for a similarly reliable and flexible mPRO™ solution for the pharmaceutical industry.

5. Conclusion

The mPRO™ solution enables the reliable collection of patient data in clinical trials via a mobile phone. Using secure mobile networks provided by the world's largest provider of such networks (Vodafone), the information entered in the eDiary or acquired from compatible Bluetooth medical devices is automatically transmitted to the trial server where it is analysed in real time, ensuring that any significant data are identified at the earliest possible opportunity.

The use of mobile phones for clinical trials ensures that the set-up and roll-out phases are extremely efficient. Most of the logistical problems which arise with the use of PDAs, such as the distribution, maintenance and recovery of devices, are eliminated. The mobile phone is a consumer-quality, ubiquitous device, which is much cheaper than a PDA. There is no need for training to familiarise the subjects with the use of the technology, as with PDAs. A multi-lingual capability has also been built into the mPRO™ solution.

The progress of any on-going trial can be monitored by reviewing the trial dashboard which provides KPI information such as recruitment, compliance and data submission rates. The dashboard continuously updates automatically, so that primary outcomes and data can be monitored in real time. Active, real-time compliance monitoring leads to high-integrity data. If needed, authorised staff can communicate securely with study patients through mPRO™'s encrypted messaging system.

mPRO™ offers a scalable platform which allows high volumes of patient data to be securely transferred and analysed in real-time, leading to a cost-effective, flexible and efficient solution for large clinical trials. At the beginning of 2009, mPRO™ is being adopted by the pharmaceutical industry and CROs in several new studies, with many more in the pipeline. The mobile phone is now a familiar device throughout the world. With Vodafone, t+ Medical's partner, running the world's largest data infrastructure, there is no geographical limitation to the use of mPRO™ for clinical trials.

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